

AD _____

Award Number: DAMD17-98-1-8302

TITLE: Compact Gamma Camera System for Breast Cancer Imaging

PRINCIPAL INVESTIGATOR: Stephen Derenzo, Ph.D.

CONTRACTING ORGANIZATION: University of California
Berkeley, California 94720

REPORT DATE: July 2000

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20010509 030

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE July 2000	3. REPORT TYPE AND DATES COVERED Annual (1 Jul 99 - 30 Jun 00)		
4. TITLE AND SUBTITLE Compact Gamma Camera System for Breast Cancer Imaging			5. FUNDING NUMBERS DAMD17-98-1-8302	
6. AUTHOR(S) Stephen Derenzo, Ph.D.			8. PERFORMING ORGANIZATION REPORT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of California Berkeley, California 94720 E-MAIL: sederemzo@lbl.gov				
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES <div style="text-align: center; padding: 10px 0;">Report contains color photos</div>				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) The goal of this project is the development of a compact solid-state gamma camera specifically designed to image metabolically active tumors in the breast and axillary nodes with the highest possible detection efficiency and spatial resolution. We have developed or purchased final versions of all major components of the proposed compact solid-state gamma camera: collimators, CsI(Tl) scintillator arrays, special low-noise silicon photodiode arrays, and custom integrated circuit readout chips. A prototype detector module was successfully assembled and interfaced to a computer. Based on results to date, it appears that our compact camera design will yield very similar performance to traditional SPECT cameras. However, for the application of breast and axillary node imaging, our compact design will have the advantages of: (1) more potential imaging angles, (2) shorter imaging distances and hence higher image quality, and (3) lower cost, making the camera more readily available. Once completed, the new camera may help make scintimammography widely available as a valuable complement to traditional breast cancer screening and diagnostic techniques.				
14. SUBJECT TERMS Breast Cancer			15. NUMBER OF PAGES 10	
17. SECURITY CLASSIFICATION OF REPORT Unclassified			16. PRICE CODE	
			20. LIMITATION OF ABSTRACT Unlimited	
18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified		19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified		
NSN 7540-01-280-5500				

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

S.E.D. Where copyrighted material is quoted, permission has been obtained to use such material.

S.E.D. Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

S.E.D. Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

N/A For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Stephen Derenzo July 31, 2000
PI - Signature Date

4. TABLE OF CONTENTS

1. Cover.....	1
2. SF 298	2
3. Foreword	3
4. Table of Contents	4
5. Introduction.....	5
6. Body.....	5
7. Key Research Accomplishments.....	8
8. Reportable Outcomes.....	8
9. Conclusions	8
10. References	9
11. Appendices	9

5. INTRODUCTION

The goal of this project is the development of a compact solid-state gamma camera specifically designed to image metabolically active tumors in the breast and axillary nodes with the highest possible detection efficiency and spatial resolution. The compact design (1) allows for a larger number of oblique views, (2) provides shorter imaging distances which results in improved spatial resolution and (3) reduces cost, which will make the instrument more widely available to the medical community.

6. BODY OF THE PROGRESS REPORT

Tasks proposed for months 12-24:

- Fabricate custom integrated circuits containing charge amplifiers and WTA crystal identifier circuits (months 1-18)
- Assemble camera (collimator, crystal arrays, diode arrays, integrated circuit readout, flex strip output connections) (months 9-24)
- Interface camera to computer (months 18-24)
- Test system using calibration pulses and small ^{57}Co sources (months 20-24)

CsI(Tl) Crystal Arrays

Two CsI(Tl) $12 \times 20 \text{ cm}^2$ crystal arrays with a depth of 5 mm and optically-isolated $3.0 \times 3.0 \text{ mm}^2$ pixels were previously purchased. These have been successfully cut into 32 smaller 8×8 pixel arrays consisting of 64 pixels each. The average dimensions on these smaller arrays is $24.2 \times 24.2 \text{ mm}^2$, sufficiently close to the ideal $24.0 \times 24.0 \text{ mm}^2$ to fulfill our imaging needs.

Silicon Photodiode Arrays

We have successfully fabricated, diced, tested, and passivated 64-pixel (8×8 element) silicon PIN photodiode arrays. These arrays are larger versions of the 12-pixel (3×4 element) arrays we had previously developed [1]. The new arrays maintain the same $3.0 \times 3.0 \text{ mm}^2$ pixel size and per-pixel capacitance of about 2 pF.

The 34 arrays diced from the 5 most promising silicon wafers provided a total of 2176 pixels with a 98.5% yield of "good" pixels (good being defined as $<100 \text{ pA}$ leakage current at room temperature and 50 V bias). These 2143 good pixels demonstrate an extremely low leakage current of $28 \pm 7 \text{ pA}$ (average \pm standard deviation) at room temperature and 50 V bias, about an order of magnitude better than the best 64-pixel arrays that are commercially available. These data are summarized in the histogram presented in Figure 1. We now have in our possession about 25 arrays whose performance makes them excellent candidates for the final 16-module camera.

Photodiode quantum efficiency for the 540 nm emission wavelength of CsI(Tl) has been observed in preliminary measurements to be greater than 75%, and we anticipate that more accurate observations will yield efficiencies as high as 90%. Based on measurements made with our 12-pixel arrays, we anticipate that at room temperature and a peaking time of 4–8 μs , the measured noise will be as low as 140 e^- rms. This is entirely adequate for our imaging needs. passivated

Printed Circuit Boards

We had previously designed and ordered prototype 24 x 24 mm² ceramic circuit boards to be used to mount both the silicon photodiode arrays and our custom integrated circuit (IC) readout chips. We further designed and ordered prototype 24 x 24 mm² multilayer circuit boards that can be mounted on top of the ceramic circuit boards. These multilayer circuit boards host the custom IC readout and control lines and as well as bypass capacitors, a metal cover to protect and EM shield the IC, and connectors for plugging an individual module into the motherboard (Figure 2). Based on mechanical and electrical experimentation with the prototype custom circuit boards, we have substantially redesigned and improved both boards for the final camera and are now in possession of the final versions.

We have completed the schematic design for the motherboard, including hardware for interfacing with individual modules as well as with the computer digital acquisition board (Figure 2). All components that must be loaded onto this board have been specifically identified, including resistor networks, peak detect hardware, and electronically-adjustable potentiometers. We are currently doing the layout design for this board and expect to have the final version fabricated and shipped to us by late September.

The newest version of our custom IC readout chip must undergo thorough testing to verify its functionality and provide quantitative measures of its performance. To this end we have designed and fabricated a custom printed circuit board whose purpose is to provide an excellent testing environment to analyze and debug the IC. This board has been fabricated and is performing exactly as expected in preliminary tests with the custom IC.

Custom Integrated Circuit Readout Chip

We had previously developed a custom integrated circuit chip containing 64 low-noise charge amplifiers and pulse shapers, a 64-channel winner-take-all (WTA) crystal identifier circuit, address electronics, and computer control of both the shaping time and gain of the 64 individual amplifiers. Based on testing and experimentation with this version of the chip, we had refined the design of both the low-noise charge amplifiers/pulse shapers and the WTA crystal identifier. This culminated in two new 16-channel prototype ICs (one for the amplifiers and one for the WTA) which were then thoroughly tested and debugged.

Based on those results, we have completed our design of the final version of the 64-channel custom readout IC. This IC incorporates both an improved array of 64 charge amplifiers/pulse shapers and an improved 64-input WTA circuit. The IC has been successfully fabricated, diced from its wafers, had its backside coated with gold, and been wirebonded to our custom IC test boards. Preliminary testing using computer control of the test board and IC is underway and has already shown that the IC meets performance expectations in the following ways: (1) power consumption is nominal, (2) rise and fall times can be externally adjusted, (3) the gain of each pre-amplifier can be externally adjusted, (4) the photodiode dark current compensation in each pre-amplifier can be externally adjusted, (5) qualitatively electronic noise looks acceptable, (6) the WTA circuitry correctly outputs the analog signal with the greatest amplitude, (7) the WTA circuitry produces the correct digital address for the channel with the largest analog signal, (8) the operational mode and noise-suppression threshold of the WTA can be externally controlled, and (9) the IC only responds to commands containing the correct identifier sequence (thus allowing multiple ICs on the same bus to be controlled separately). Based on these promising preliminary results and

quantitative measurements made on the latest 16-channel prototype ICs, we anticipate that this 64-channel IC will prove entirely sufficient for our imaging needs.

Collimators

Based on previous computer simulations, we have developed three collimator designs that will work well for breast cancer imaging. We have ordered and now have in our possession lead hexagonal hole, parallel channel collimators that cover an area $10 \times 10 \text{ cm}^2$ (more than sufficient to cover a plane of $16 \times 24 \times 24 \text{ mm}^2$ detector modules). All designs have 1.5 mm diameter holes and a septal thickness of 0.25 mm but vary in length: 23.5 mm (all purpose), 16.5 mm (high sensitivity), and 13.0 mm (ultra high sensitivity).

Assembly Procedures

The final camera assembly and construction will involve a large number of steps that must be carried out with great precision and care. Among the steps that must be performed to complete an individual detector module are: (1) the ceramic circuit board and the multilayer circuit board must be glued together, (2) the IC, metal shield, bypass capacitors, and connectors must be loaded onto the ceramic board/multilayer board assembly, (3) the custom photodiode array must be attached to the ceramic board via 64 accurately placed drops of conductive epoxy (1 for each pixel), (4) the custom photodiode surface must be protected by filling the photodiode-ceramic board air gaps with an underfill epoxy, (5) additional wirebonds must be made on the ceramic board/multilayer board/custom IC/custom photodiode assembly, and (6) a CsI(Tl) array must be attached to the custom photodiode array via optically-transparent epoxy. During all of these steps it is of prime concern that all components be precisely aligned, that the module be made mechanically durable, and that no components be damaged either mechanically, chemically through contact with epoxy, or thermally during epoxy curing.

We have successfully identified the means by which to accomplish all of these assembly procedures. Our ceramic boards and multilayer boards are currently being glued together by a commercial company that has already produced excellent prototypes. We have identified a commercial company that can load the IC and all components onto the ceramic board/multilayer board assembly and will have them perform this work once the ceramic board/multilayer board assemblies are returned to us. We will perform all of the remaining steps ourselves. The necessary epoxies have been identified and in experiments proved to perform as needed. All assembly jigs and stencils needed to align components and to apply epoxy precisely have been constructed and tested. Partial modules consisting of a ceramic board, photodiode array, and CsI(Tl) have been assembled to determine the correct procedures by which to construct our modules without damaging the sensitive and much-exposed-to-epoxy photodiode arrays. We can now confidently assemble modules with precisely-aligned components that demonstrate no degradation in the behavior of our custom photodiode arrays.

The following tasks were proposed after month 24 and will be described in the final progress report:

- Measure intrinsic spatial resolution with and without scatter (months 24-30)
- Measure pulse height resolution with and without scatter (months 24-30)
- Measure planar sensitivity and count rate performance (months 28-36)

- Acquire images of isotope distributions using standard plastic phantoms (months 28-36)

7. KEY RESEARCH ACCOMPLISHMENTS

- Five high purity silicon wafers were fabricated and diced to produce 34 64-pixel photodiode arrays with a 98.5% yield of good pixels.
- Fabrication of the custom 64-channel integrated circuit readout chip was completed and initial testing shows that all functions are operational.
- Assembly procedures for the detector modules were developed, including gluing custom circuit boards together, mounting and wirebonding the integrated circuit, mounting the photodiode array, protecting the photodiode array with underfill epoxy, making additional wirebonds between the circuit boards and the photodiode array, and optically bonding the CsI:Tl scintillator array to the photodiode array.
- Three printed circuit boards were designed and fabricated: (1) a test board for the custom integrated circuit (IC), (2) a ceramic board for mounting the photodiode array and hosting the IC fan in, and (3) a multilayer board for routing the IC output and control lines.

8. REPORTABLE OUTCOMES

Gruber GJ, Moses WW and Derenzo SE. Monte Carlo simulation of breast tumor imaging properties with compact, discrete gamma cameras. *IEEE Trans. Nucl Sci.* 1999; NS-46:2119-2123.

Gruber GJ, Moses WW, Derenzo SE, Holland SE, Pedrali-Noy M, Krieger B, Mandelli E, Meddeler G, Wang NW, Ho MH and Tindall CS. Performance of a Compact 64-Pixel CsI(Tl)/Si PIN Photodiode Imaging Module with IC Readout. To be presented at the 2000 IEEE Medical Imaging Conference:

Pedrali-Noy M, Gruber GJ, Krieger B, Mandelli E, Meddeler G, Moses WW and Rosso V. PETRIC—A Positron Emission Tomography Readout IC. To be presented at the 2000 IEEE Medical Imaging Conference

Moses W, Pedrali-Noy M and Beuville E. Custom integrated circuit for multi-channel solid-state detector readout. LBNL Invention Disclosure Report No. IB-1472P, 2000. patent applied 2000

9. CONCLUSIONS

We have developed or purchased final versions of all major components of the proposed compact solid-state gamma camera: collimators, CsI(Tl) scintillator arrays, special low-noise silicon photodiode arrays, and custom integrated circuit readout chips. Small prototype detector modules were successfully assembled using prototype components and interfaced with a computer. Testing demonstrated both good energy resolution (10.7% for 140 keV) and good spatial resolution (5.9 mm fwhm at 5 cm imaging distance). Monte Carlo simulations have helped optimize the final camera design, supporting the use of high-sensitivity hexagonal hole collimators and $3.0 \times 3.0 \text{ mm}^2$ pixels while demonstrating that cooling the electronics is not necessary [2].

Based on results to date, it appears that our compact camera design will yield very similar performance to traditional SPECT cameras. However, for the application of breast and axillary node imaging, our compact design will have the advantages of: (1) more potential imaging angles, (2) shorter imaging distances and hence higher image quality, and (3) lower cost, making the camera more readily available. Once completed, the new camera may help make scintimammography a valuable complement to traditional breast cancer screening and diagnostic techniques.

10. REFERENCES

- [1] Gruber GJ, Moses WW, Derenzo SE, Wang NW, Beuville E and Ho MH. A discrete scintillation camera using silicon photodiode readout of CsI(Tl) crystals for breast cancer imaging. *IEEE Trans. Nucl Sci.* 1998; NS-45:1063–1068.
- [2] Gruber GJ, Moses WW and Derenzo SE. Monte Carlo simulation of breast tumor imaging properties with compact, discrete gamma cameras. *IEEE Trans. Nucl Sci.* 1999; NS-46:2119-2123.

11. APPENDICES

Figures Referenced in Section 6, Body of the Progress Report

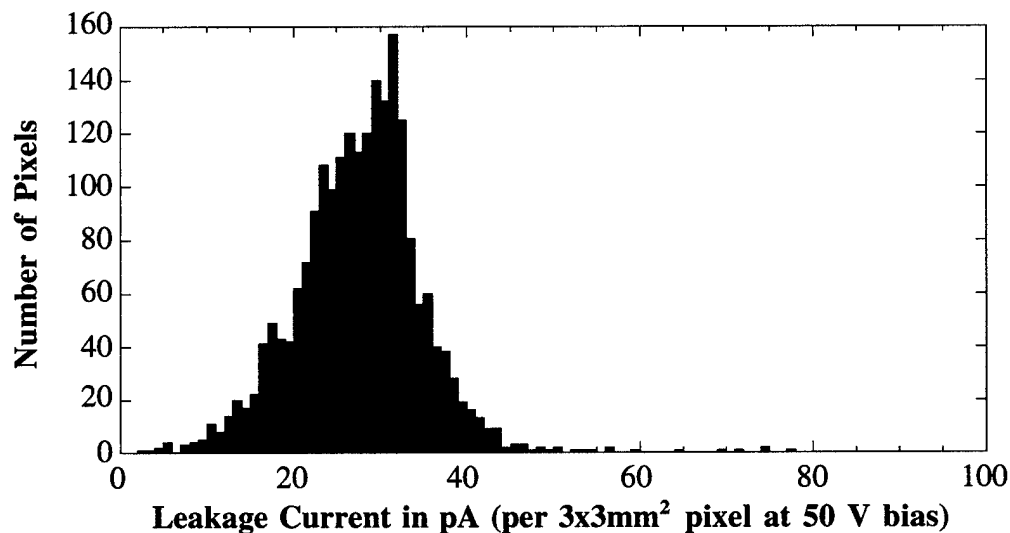


Figure 1. Histogram of leakage currents for 2143 pixels (out of a total of 2176) in 34 arrays diced from five silicon wafers. Only 23 pixels had a dark current greater than 100 pA. The average leakage current is about an order of magnitude better than the best 64-pixel arrays that are commercially available.

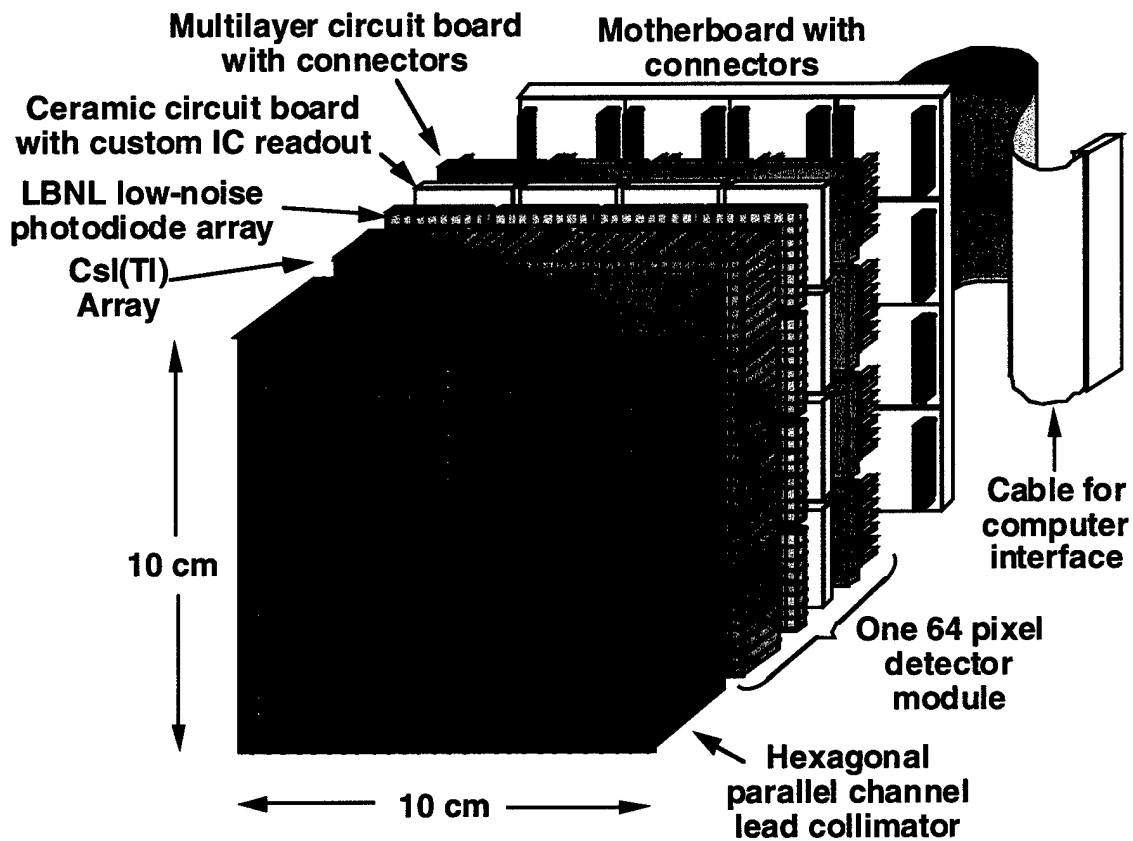


Figure 2. Schematic of 1024-pixel compact gamma camera.